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Environmental Contributions to Autism: Explaining the Rise in Incidence of Autistic Spectrum Disorders

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Abstract

The incidence of autism spectrum disorders, a heterogenous group of neurodevelopmental disorders is increasing. In response, there has been a concerted effort by researchers to identify environmental risk factors that explain the epidemiological changes seen with autism. Advanced parental age, maternal migrant status, maternal gestational stress, pregnancy and birth complications, maternal obesity and gestational diabetes, maternal vitamin D deficiency, use of antidepressants during gestation and exposure to organochlorine pesticides during pregnancy are all associated with an increased risk of autism. Folic acid use prior to pregnancy may reduce the risk of autism. Exposure to antenatal ultrasonography, maternal gestational cigarette and alcohol use do not appear to influence the risk of autism in offspring. There is little evidence that exposure to environmental toxins such as thimerosal, polybrominated diphenyl ethers and di-(2-ethylhexyl) phthalate in early childhood increases the risk of autism. Apart from birth complications, the current evidence suggests that the majority of environmental factors increasing the risk of autism occur in the antenatal period. Consistent with the rise in incidence in autism, some of these environmental factors are now more common in developed nations. Further research is required to determine how these environmental exposures translate to an increased risk of autism. Understanding how these exposures alter neurodevelopment in autistic children may inform both the aetiopathogenesis and the strategies for prevention of autism.

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Key words

autism; autism spectrum disorder; environment; risk factors

Background

Autism spectrum disorders (ASD) are a heterogenous group of neurodevelopmental disorders affecting approximately one percent of children.[1,2] The characteristic triad of impairments in communication, social difficulties and restricted interest or repetitive behaviours, together with difficulties in emotional processing, sensory-perceptual processing, and motor proficiency, adversely affect developmental trajectories and family functioning from the early years.[3] Impact routinely continues across the lifespan adversely affecting independence, education, and participation in school, work, and community life.[4] Although early intervention can benefit some children with autism,[5] the ongoing disability experienced by many individuals is severe. The neurodevelopmental changes responsible for ASD arise from a combination of genetic, epigenetic and environmental factors.[6,7]

Of great concern, the incidence of autism is increasing. Whilst a proportion of the increase is attributable to the broadening of diagnostic boundaries and improved identification of ASD cases,[8] it is widely viewed that there is also a true increase in the incidence and prevalence of autism.[2] For example in California, cases of autism diagnosed by developmental services rose from 6.2/10000 births in 1990 to 42.5/10000 births in 2001. Broadening of diagnostic criteria and earlier age of diagnosis accounted for almost 70% of the increase in incidence, however almost one third of the increase in incidence of ASD was unexplained by these factors.[9] This changing epidemiology has resulted in a concerted research effort to identify non-genetic (environmental) factors that explain the increase in incidence of ASD. Identification of environmental risk factors will provide opportunities to both better understand the aetiopathogenesis of ASD and to implement strategies that lead to prevention of the disorder.

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Parental risk factors for autism prior to pregnancy

Parental migration and advanced parental age are both associated

with an increased risk of having offspring with ASD. A systematic review by Dealberto (2011)[10] reported an increase in relative risk (RR) of autism in the offspring whose mothers were of foreign birth. The relative risks varied depending on ethnicity, with offspring of dark skinned migrants at particularly high risk of autism. An earlier meta-analysis by Gardener and colleagues[11] also reported an increased risk of autism for children who had mothers born abroad. In an English case control study of 428 children with autism, mothers born in the Caribbean region had approximately a 10 fold risk of having a child with ASD compared to English born white mothers.[12] In a large Swedish case control study, mothers who had immigrated around the time of pregnancy had the greatest increased risk of having a child with autism.[13]

It has been suggested that the increase in risk of autism in the offspring mothers who are of dark skinned ethnicity and have migrated to Northern European countries supports the hypothesis that maternal vitamin D deficiency is the mediating factor.[14] Vitamin D deficiency is an attractive candidate risk factor for autism.[15] It has been shown to have a key role in foetal brain development[16] and the incidence of autism has been shown to increase with an increase in latitude, where vitamin D deficiency is most likely to occur due to reduced exposure to sunlight.[17] However, the migration studies suggest that the act of migration was an important independent risk factor for offspring with autism.[12,13] Maternal stress during pregnancy has also been shown to be associated with an increased risk of autism[18] and it is a plausible mediating factor for the association between migrant mother and ASD.

Advanced parental age is another risk factor where there is robust evidence from two meta-analyses finding a significant association with an increased risk of autism in the offspring. Comparing mothers who were greater than 35 years of age with mothers aged between 25 to 29 years, the relative risk (RR) for autism in the offspring after adjusting for paternal age was 1.31 (95% Confidence Interval (CI) =1.19-1.45).[19] In a meta-analysis of paternal age and risk of autism, Hultman and colleagues (2011) reported that compared to fathers aged ≤ 29 years, the RR for autism in offspring were 1.22 in fathers aged 30-39 years (CI=1.05-1.42), 1.78 in fathers aged 40-49 years (CI=1.52-2.07) and 2.46 for fathers aged 50 and older (CI=2.20-2.76).[20]

The association between advanced maternal age and increased risk of autism in offspring may be explained by the increased likelihood of maternal gestational obesity and diabetes[21] and increased risk of antenatal or perinatal complications in older mothers.[11,22] Increased likelihood of genetic mutations might explain the increased risk of ASD in older fathers. Spermatogonia undergo cell division every sixteen days, resulting in approximately 200 divisions by the age of 20 years and 660 divisions by the age of 40 years.[23] Each time the cell divides, the replication of the genome introduces the possibility of copy error mutations, such as point mutations, or larger copy number variants (e.g. deletions, amplifications). Animal experimental studies have recently confirmed that the offspring of older males have an increased risk of *de novo* copy number variants,[24] and these regions contain genes implicated in both schizophrenia and autism. Apart from mutations that change the DNA sequence, epigenetic mechanisms may also be involved.[25]

Risk factors for autism identified in pregnancy.

In a meta-analysis of 40 studies of pregnancy complications which included cohorts with a total of 1086271 participants, maternal gestational diabetes was associated with a two-fold risk of autism, maternal medication use during pregnancy was associated with a 46% increased risk of autism and psychiatric medication use during pregnancy was significantly positively associated with Autism (RR=1.68). In the Childhood Autism Risks from Genetics and the Environment (CHARGE) study, children with autism whose mothers had diabetes during pregnancy had lower scores of expressive language compared to children with autism whose mothers had no metabolic conditions.[21] Evidence is emerging that maternal metabolic conditions have a broad adverse impact on offspring neurodevelopment. Compared to normal gestational weight, obesity in pregnancy is associated with delayed cognitive development in offspring.[26] At this time, the biological mechanisms underpinning the association between maternal obesity in pregnancy and offspring neurodevelopmental delays are unclear.

Maternal stress during pregnancy has long been proposed as a risk factor for autism.[27] In the most convincing natural experiment, the prevalence of autism in the offspring of mothers exposed to severe weather events in Louisiana was 13.32/10000 compared to a much lower prevalence of 4.49/10000 in controls.[18] Increased cortisol levels in the amniotic fluid and decreased placental blood flow are two mechanisms proposed to explain how stress may alter neurodevelopment.[28] Since the introduction of selective serotonin reuptake inhibitors (SSRIs), there has been widespread use of antidepressants in developed countries. In a case control study of gestational use of antidepressant medication and risk of autism, 6.7% of mothers of children with autism used SSRIs compared to 3.3% of mothers of typically developing children. After adjusting for markers of mental health such as diagnosis and health service usage, use of SSRIs during pregnancy remained significantly associated with risk of autism.[29] The effect of antidepressant and other medications commonly taken in pregnancy on neurodevelopment requires further research.

Gestational exposure to toxins in the environment have been identified as increasing the risk of autism in offspring. Living in close proximity to a freeway was associated with a twofold increase in risk of autism (Odds Ratio and 95% CI 1.86; 1.04-3.45) presumably as a result of air pollution.[30] Gestational exposure to organochlorine pesticides, specifically endosulfan and dicofol, have been associated with a six-fold increased risk of autism in the offspring.[31] In spite of the strong association, it is unlikely that organochlorines are responsible for the increase in incidence of autism in developed countries. The use of these pesticides has become highly regulated and in many countries they are banned altogether.

Some environmental exposures in pregnancy have been shown to have no association with increased risk of autism. Reassuringly, the use of ultrasound in pregnancy is not associated with increased risk of ASD.[32] Although gestational alcohol and cigarette use is associated with a broad range of adverse health outcomes in the offspring, no association was found between these exposures and

increased risk of autism.[33,34] Finally, Beard and colleagues (2011) proposed that excess maternal folic acid use to prevent neural tube defects might account for the increase in incidence of autism.[35] This hypothesis has not been supported by the available evidence. In fact, a report from the CHARGE study found that the risk of autism decreased in mothers who had taken folic acid and vitamins in the three months prior to pregnancy and the first month of pregnancy.[36] The authors suggested that peri conception vitamin and folic acid use may reduce the risk of autism in offspring.

Perinatal and neonatal complications and risk of autism

In a recent meta-analysis, Gardener and colleagues examined more than 60 perinatal and neonatal factors and autism risk. Perinatal factors associated with the autism risk included abnormal foetal presentation, umbilical-cord complications, birth injury or trauma, maternal hemorrhage, low birth weight, small for gestational age, low 5-minute Apgar score, meconium aspiration, neonatal anemia, ABO or Rh incompatibility, and hyperbilirubinemia.[22] Premature birth is also a risk factor for altered neurodevelopmental trajectories including autism.[37] As there have been significant advances in obstetric care, it is counter-intuitive to consider that an increase in autism incidence might be explained by perinatal complications. However, improved obstetric care has resulted in the live births of babies that previously may not have survived. In light of this, perinatal complications may play a role in increasing the incidence of autism.[38]

Risk factors operating in early childhood

Compared to environmental risk factors for autism that have been identified prior to and during pregnancy, the evidence for risk factors in early childhood is less convincing. Multiple studies of exposure to thimerosal, a mercury containing preservative that was used in vaccines had reported no increased risk of ASD in children from American samples.[39,40] This finding has also been found in studies consisting of European[41,42] and Japanese cohorts.[43] Consistent with this finding, the CHARGE study reported no difference in the total blood mercury concentrations of children with ASD and controls.[9] Polybrominated diphenyl ethers (PBDEs) are flame retardants that are widely used in developed countries and have been shown to affect neurodevelopment in animal models. The CHARGE study examined this exposure and found that PBDE levels were high in both children with ASD and typically developing children and there was no difference in levels between the two groups.[9]

In a case-control study of 48 children with ASD and 45 matched controls, primary and secondary metabolites of di-(2-ethylhexyl) phthalate (DEHP) was found to be higher in children with autism.[44] Phthalates are used as plasticizers, solvents and additives in many consumer products such as vinyl flooring, wall coverings and food containers.[45] Testa and colleagues (2012) proposed that through endocrine disruption, phthalates may play a role in altering neurodevelopment of neurotransmitter systems.[44] A prospective study showed that children aged 4-9 years with higher prenatal phthalate exposure performed poorer on tests of executive functioning and externalising behaviours with increased risk of problems such as aggression, attentional weaknesses and conduct problems however autism was not an outcome of this study.[46] Phthalates need to be investigated in a larger study to determine the role if any that they might have in the aetiopathogenisis of autism.

Toxins produced by Clostridia and Desulfovibrio bacteria in the gut have also been proposed as candidate risk factors for regressive autism.[47,48] It has been hypothesised that use of antibiotics has lead to an alteration in the bowel flora of some children where there has been an overgrowth of Clostridia and Desulfovibrio bacteria which are resistant to penicillin and cephalosporins. Examination of the bacteria in the stools of children with ASD compared to controls showed differences in the bowel flora of the two groups.[49,50] Further research is necessary to show evidence supporting these hypotheses.

Discussion

Autism, a persistent and frequently severely disabling neurodevelopmental disorder, is rising in incidence. Concurrent with the change in the epidemiology of autism, there have been societal changes, particularly in developed countries that have increased the likelihood of exposure to some of the identified environmental risk factors. The risk factors for which the most evidence exists are shown in **Table 1**.

Parental migration, advanced parental age, maternal stress, gestational antidepressant use and gestational metabolic conditions have all been shown to be associated with an increased risk of autism in offspring. These factors have increased in the population with recent changes that have occurred in developed nations. With the exception of air pollution and organochlorine pesticides, there is limited or no evidence for external toxins being associated with increased risk of autism.

Autism is just one of a number of serious adverse health conditions that has risen in prevalence in developed countries. Like autism, obesity, cardiac disease and diabetes mellitus have also substantially increased in many countries around the world. It is plausible that the rise in all of these health problems is in part attributable to common mechanisms such as immune dysregulation interacting with lifestyle factors. A common challenge to combating the rising prevalence of these chronic disorders is modifying the risk factors so as to reduce their incidence and their associated burden of disease.

Research is now needed to determine why exposure to environmental factors results in the autism phenotype in some children and not others. It is clear that immune system regulation and oxidative stress in children with autism is different to that of typically developing children.[51-53] However, the epidemiology suggests that the main environmental risks for autism occur prior to or during pregnancy. Understanding how these exposures alter neurodevelopment in autistic children may inform both the aetiopathogenesis and the strategies for prevention.

Table 1. Summary of Environmental contributions to autism: Influence of early life exposures

Exposure	Critical window[a]	Shape of DRC[a]	Presumed mechanism of action	Strength of evidence	
				Animal studies	Human studies
Advanced Maternal Age	Pre-conception	Linear	Increased risk of birth complications and gestational metabolic conditions	No	Yes
Advanced Paternal Age	Pre-conception	Linear	Increased risk of de novo point mutations, or larger copy number variants occurring during meiosis	Yes	Yes
Migration	Pre-conception and *in utero*	Highest risk in year before conception	Maternal Stress	Yes	Yes
Vitamin D Deficiency	Peri-conception and *in utero*	Unknown	Lack of vitamin D altering typical neurodevelopment	Yes	No
Maternal Metabolic conditions (Gestational obesity and diabetes)	*in utero*	Higher BMI associated with increased risk.	Unknown	Yes	Yes
Maternal antidepressant use	*in utero* particularly first trimester	Unknown	Alteration in 5-HT signalling in offspring	Yes	Yes
Maternal Stress	*in utero* particularly second and third trimester	Unknown	Elevated corticosteroids in amniotic fluid	Yes	Yes
Organochlorine pesticides	*in utero* particularly first trimester	Linear	Organochlorine pesticides alters gamma amino-butyric acid(GABA) mediated neurotransmission which is important in gestational brain development	Yes	Yes
Birth complications including prematurity	Ante and Perinatal	Not Applicable	Direct trauma to brain. Elevated conjugated bilirubin which is toxic to the cerebellum	Yes	Yes

[a]Developmental stage where exposure increases the risk of the clinical outcome, e.g.: *in utero*, w to y weeks gestation; early postnatal life, etc. [b]Shape of dose-response curve, e.g.: linear, U shaped, inverted U shaped, etc. Indicate whether data comes from animal, *in vitro*, or human studies.

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